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(54) Title: METHODS AND COMPOSITIONS OF (+) DOXAZOSIN FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA AND ATHEROSCLEROSIS

(57) Abstract

Methods and compositions are disclosed utilizing the optically pure (+) isomer of doxazosin. This compound is a potent drug for the treatment of benign prostatic hyperplasia while avoiding the concomitant liability of hypotensive effects associated with the racemic mixture of doxazosin. The optically pure (+) isomer of doxazosin is also useful for the treatment and prevention of atherosclerosis and other conditions related to elevated serum LDL and cholesterol levels, such as coronary artery disease, without the concomitant liability of adverse effects associated with the racemic mixture of doxazosin.

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METHODS AND COMPOSITIONS OF (+) DOXAZOSIN  
FOR THE TREATMENT OF BENIGN PROSTATIC  
HYPERPLASIA AND ATHEROSCLEROSIS

BACKGROUND OF THE INVENTION

5        This invention relates to novel compositions of matter containing optically pure (+) doxazosin. These compositions are of utility in the treatment of patients with benign prostatic hyperplasia (BPH) or in the treatment of patients with elevated serum low density lipoprotein (LDL) levels. Pure (+) doxazosin exhibits little of the hypotensive activity associated with the (-) enantiomer and is therefore superior to racemic doxazosin for these indications. Also disclosed are methods for treating BPH and 15      elevated LDL in a human while avoiding the hypotensive effects that are associated with the racemic mixture of doxazosin by administering the (+) isomer of doxazosin to said human.

20       The active compound of these compositions and methods is an optical isomer of doxazosin, which is described by Young and Brogden in Drugs 35, 525-541 (1988) and United States Patent No. 4,188,390. Chemically, the active compound is the (+) isomer of 25      4-amino-2-[4-(1,4-benzodioxan-2-carbonyl)piperazin-1-yl]-6,7-dimethoxyquinazoline also known as 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxan-2-yl)carbonyl]piperazine hereinafter referred to as doxazosin.

30       (+) Doxazosin, which is the subject of the present invention, is available commercially only as the 1:1 racemic mixture. That is, (+) doxazosin is

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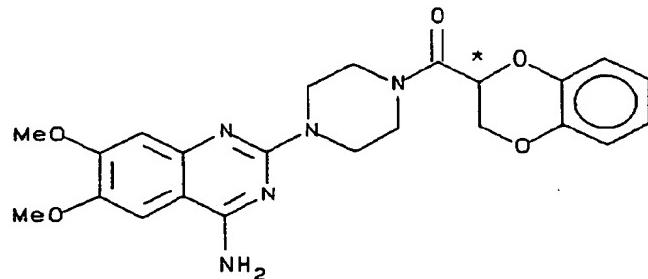
available only as a mixture of optical isomers, called enantiomers. The racemic mixture of doxazosin is commercially available for administration as a methanesulfonate (mesylate) salt, but extensive 5 pharmacology has been published on the hydrochloride salt as well.

Many organic compounds exist in optically active forms, i.e. they have the ability to rotate the plane 10 of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the 15 compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. There is no correlation between nomenclature for the absolute stereochemistry and for the rotation of an enantiomer. Thus, D-lactic acid 20 is the same as (-) lactic acid, and L-lactic acid is (+). For a given chemical structure, these compounds, called stereoisomer, are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an 25 enantiomer, and a mixture of such isomers is often called an enantiomeric or racemic mixture.

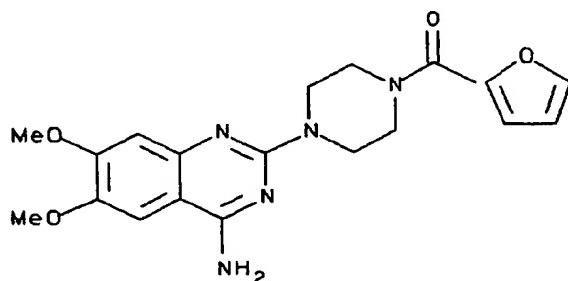
Doxazosin (I) is a representative of a group of drugs that block  $\alpha_1$  adrenoceptors.  $\alpha_1$  Receptors are innervated by postganglionic sympathetic neuronal 30 fibers and are located in many body systems, including the cardiovascular system and the urinary tract. Evidence is now beginning to accumulate that

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there are subtypes of  $\alpha_1$  receptors, making  $\alpha_1$  adrenergic receptors a family of recognition units rather than a monolithic element. Bylund [FASEB J. 6, 832-839 (1992)] has presented evidence that there  
 5 are at least three presently differentiable  $\alpha_1$  receptor subtypes. Prazosin (II), an achiral analog of doxazosin, is reported to have similar affinities for each of these subtypes.



I



II

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Doxazosin has a single chiral center located on the carbon adjacent to the carboxyl group (shown in formula I). This gives rise to a pair of enantiomers which have been resolved by Ley et al. [Recent Advances in Chiral Separations, Steven and Wilson Editors, Plenum Press, New York (1991) pages 97-103] on an analytical scale (0.52  $\mu$ g), but there are no reports in the literature of a preparative-scale separation of the enantiomers.  
 15

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Although the inventor does not wish to be bound by a theoretical construct, it is possible that the beneficial effects of (+) doxazosin in increasing urine flow and bladder evacuation and in improving serum lipid profiles with minimal effects on such other cardiovascular parameters as blood pressure and heart rate arise from the selective inhibition of a specific subset of  $\alpha_1$  receptors by the (+) isomer as compared to its enantiomer, which may preferentially inhibit those subsets involved in regulating blood pressure.

The racemic mixture of doxazosin is presently used primarily as an antihypertensive agent. Doxazosin's oral bioavailability is good and the plasma half life in man is approximately 10 hours following both oral and intravenous administration. There are reports that the administration of racemic doxazosin leads to modestly decreased total cholesterol and LDL levels. [Young & Brogden Drugs 35, 525-541 (1988) and references therein.] There is also a report of the use of prazosin (II) to treat BPH [Hedlund et al., J. Urology 130, 275-278 (1983)]. However, neither of the drugs has enjoyed widespread use for either BPH or improvement of serum lipid profiles because of the cardiovascular effects that are the primary result of their administration.

A troublesome cardiovascular problem related to the use of previously known  $\alpha_1$  receptor antagonists for the treatment of BPH and the improvement of serum lipid profiles is their hypotensive activity, which is particularly reflected in the problem of orthostatic hypotension. Symptomatic orthostatic

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hypotension is most likely to occur with high initial doses of earlier  $\alpha_1$  antagonists or may occur when the dose is increased rapidly. A modest degree of fluid retention, which is another result of vasodilation,  
5 may be observed. Reflex tachycardia is also occasionally observed.

Many of the  $\alpha_1$  antagonists cause somewhat similar adverse effects. The incidence of reported side effects associated with racemic doxazosin-treated patients has varied among studies. The incidence of total side effects associated with doxazosin in patients treated for hypertension has ranged between 0 and 75%, but has generally been similar to that seen with other  $\alpha_1$ -blocking agents at dosages producing a similar reduction in blood pressure. The most frequently reported side effects have been postural hypotension, nausea, lethargy, fatigue and dizziness.  
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It would be particularly desirable to find an  $\alpha_1$  antagonist that exhibited the beneficial effect on serum lipids hinted at by the racemic mixture of doxazosin but which would not have effects on blood pressure and heart rate. It would also be desirable to find a superior and selective  $\alpha_1$  antagonist for the treatment of BPH.  
20  
25

#### SUMMARY OF THE INVENTION

It has now been discovered that the optically pure (+) isomer of doxazosin is an effective agent for the treatment of BPH that avoids the hypotensive effects of racemic doxazosin. It is also an  
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effective agent for the improvement of serum lipid profiles that avoids the adverse effects associated with the administration of the racemic mixture. The present invention also includes methods for treating 5 BPH and for treating or preventing atherosclerosis in a human while avoiding the cardiovascular effects that are associated with the racemic mixture of doxazosin, by administering the optically pure (+) isomer of doxazosin to said human.

10

DETAILED DESCRIPTION OF THE INVENTION

The present invention encompasses a method of eliciting an increase in urine flow in a human, while avoiding the concomitant liability of hypotensive effects associated with the administration of racemic 15 doxazosin, which comprises administering to a human an amount of (+) doxazosin, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to increase urine flow, but insufficient to cause the 20 hypotensive effects associated with the racemic mixture of doxazosin.

The present invention also encompasses a composition for increasing urine flow in a human, which comprises an amount of (+) doxazosin, or a 25 pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to increase urine flow but insufficient to cause the hypotensive effects associated with racemic doxazosin.

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The present invention also encompasses a method of lowering plasma cholesterol and low density lipoprotein levels in a human while avoiding the concomitant liability of adverse effects associated 5 with racemic doxazosin, which comprises administering to a human an amount of (+) doxazosin, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to lower the cholesterol and 10 LDL levels but insufficient to cause the adverse effects associated with racemic doxazosin.

The present invention also encompasses a composition for lowering serum cholesterol and low density lipoprotein in humans, which comprises an 15 amount of (+) doxazosin or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to lower serum low density lipoproteins, but insufficient to cause adverse effects associated with 20 the administration of racemic doxazosin.

The available racemic mixture of doxazosin (i.e. a 1:1 racemic mixture of the two enantiomers) possesses antihypertensive activity and provides 25 therapy and a reduction of symptoms in conditions and disorders related to hypertension. In addition, racemic doxazosin has been shown to improve the profile of serum lipoproteins in humans. Epidemiological studies have indicated that high 30 concentrations of high density lipoprotein (HDL) cholesterol are a negative risk factor for coronary artery disease, while high concentrations of low density lipoprotein (LDL) cholesterol are a positive

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risk factor. During doxazosin administration to hypertensive patients there has been a trend to an increase in high density lipoprotein cholesterol and in HDL/total cholesterol ratio and to a decrease in plasma total cholesterol and triglycerides. Changes relative to baseline were occasionally significant for HDL/total cholesterol ratio, triglycerides and total cholesterol. The effect was evident after 12 weeks' treatment and was maintained for up to 1 year.

Unfortunately, the strong hypotensive effects of racemic doxazosin make the presently available drug unattractive for the purpose of improving lipoprotein profiles in the prevention and treatment of coronary artery disease. The use of the substantially pure (+) isomer makes possible the desired favorable effect on serum lipoprotein profiles while eliciting diminished cardiovascular activity. "Cardiovascular" activity encompasses hypotension, vasodilation, tachycardia, and increased cardiac output.

The smooth muscles of the human bladder neck, bladder base, urethra and prostatic capsule are innervated sympathetically, and contraction-mediating  $\alpha$ -adrenoceptors have been demonstrated in these structures. It has been suggested that urinary retention as the result of increasing outflow obstruction in benign prostatic hyperplasia may be caused partly by stimulation of prostatic  $\alpha$ -adrenoceptors. Supporting this view, favorable results have been reported during treatment with the  $\alpha$ -adrenoceptor blockers phenoxybenzamine and prazosin.

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- Isolated human urethra contracted by noradrenaline is relaxed completely by prazosin. Furthermore, prazosin exerts an  $\alpha$ -adrenoceptor blocking effect on both human prostatic adenoma tissue and prostatic capsule tissue in vitro. Thus, if stimulation of  $\alpha$ -adrenoceptors contributes to the obstruction of benign prostatic hyperplasia, their blockade ought to be effective therapeutically, and, in fact, prazosin has been shown to improve urinary flow and bladder evacuation in patients suffering from benign prostatic hyperplasia. There are no reports of the use of doxazosin for this indication. The use of substantially pure (+) doxazosin makes possible the improvement in urinary flow and bladder evacuation without the concomitant cardiovascular activity of classical  $\alpha$ , antagonists and racemic doxazosin. It is therefore, more desirable to administer the (+) isomer of doxazosin than racemic doxazosin.
- The term "adverse effects" includes, but is not limited to hypotension, postural hypotension, nausea, lethargy, fatigue and dizziness. Side effects that have been reported with doxazosin include headache, blurred vision, edema, chest discomfort, constipation, dry mouth, sexual dysfunction, anxiety or nervousness, insomnia, palpitations, tachycardia, rash, paresthesia, muscle cramps, increased sweating, conjunctivitis, diarrhea, flatulence, dyspnea, leukopenia, neutropenia, rhinitis and increased frequency of micturition.

The term "substantially free of its (-) stereoisomer" as used herein means that the

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compositions contain a greater proportion of the (+) isomer of doxazosin in relation to the (-) isomer. In a preferred embodiment, the term "substantially free of its (-) isomer" as used herein means that the composition is at least 90% by weight of (+) doxazosin and 10% by weight or less of (-) doxazosin. In a more preferred embodiment the term "substantially free of the (-) stereoisomer" means that the composition contains at least 99% by weight of (+) doxazosin, and 1% or less of (-) doxazosin. In the most preferred embodiment, the term "substantially free of its (-) stereoisomer" as used herein means that the composition contains greater than 99% by weight of (+) doxazosin. These percentages are based upon the total amount of doxazosin in the composition. The terms "substantially optically pure (+) isomer of doxazosin" or "substantially optically pure (+) doxazosin" and "optically pure (+) isomer of doxazosin" and "optically pure (+) doxazosin" are also encompassed by the above-described amounts.

The chemical synthesis of the racemic mixture of doxazosin can be performed by the method described in U.S. Patent 4,188,390. The individual enantiomers of doxazosin may be obtained by resolution of the racemic mixture of enantiomers using conventional means. Doxazosin may be resolved with an optically active acid such as tartaric acid at the N-(1,4-benzodioxan-2-carbonyl)piperazine stage or at the final product. Alternatively the benzodioxan-carboxylic acid intermediate can be resolved with an optically active base such as brucine or  $\alpha_1$ -phenethylamine. Other standard methods of resolution

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known to those skilled in the art, including but not limited to simple crystallization and chromatographic resolution, can be used. [See for example, Stereochemistry of Carbon Compounds, E.L. Eliel, 5 McGraw Hill (1962); "Tables of Resolving Agents" Wilen and Lochmuller, J. Chromatography 113, 283-302 (1975).] Additionally, the optically pure (+) isomer can be prepared from the racemic mixture by enzymatic biocatalytic resolution. See for example, U.S. 10 Patent Nos. 5,057,427 and 5,077,217, the disclosures of which are incorporated herein by reference.

The magnitude of a prophylactic or therapeutic dose of (+) doxazosin in the acute or chronic management of disease will vary with the severity of 15 the condition to be treated, and the route of administration. The dose, and perhaps the dose frequency, will also vary according to the age, body weight, and response of the individual patient. In general, the total daily dose range, for (+) 20 doxazosin, for the conditions described herein, is from about 0.1 mg to about 20 mg, in single or divided doses. Preferably, a daily dose range should be between about 0.5 mg to about 10 mg, in single or divided doses, while most preferably, a daily dose 25 range should be between about 0.5 mg to about 5 mg, in single or divided doses. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 0.5 mg to about 1 mg, and increased up to about 10 mg or higher depending on 30 the patient's global response. It is further recommended that children, and patients over 65 years, and those with impaired renal, or hepatic function, initially receive low doses, and that they

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be titrated based on individual response(s) and blood level(s). It may be necessary to use dosages outside these ranges in some cases, as will be apparent to those skilled in the art. Further, it is noted that 5 the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient response. The terms "an amount sufficient to increase urine flow but insufficient to cause said hypotensive effects" 10 and "an amount sufficient to lower cholesterol and LDL levels but insufficient to cause adverse effects" are encompassed by the above-described dosage amounts and dose frequency schedule.

Any suitable route of administration may be 15 employed for providing the patient with an effective dosage of (+) doxazosin. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, and like forms of administration may be employed. Dosage forms include 20 tablets, troches, dispersions, suspensions, solutions, capsules, patches, and the like.

The pharmaceutical compositions of the present invention comprise (+) doxazosin as the active ingredient, or a pharmaceutically acceptable salt thereof, and may also contain a pharmaceutically acceptable carrier, and optionally, other therapeutic 25 ingredients.

The terms "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to 30 salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and

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bases and organic acids and bases. Since the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids including inorganic and organic acids.

5 Suitable pharmaceutically acceptable acid addition salts for the compound of the present invention include acetic, benzenesulfonic (besylate), benzoic, camphorsulfonic, citric, ethenesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, 10 methanesulfonic (mesylate), mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, and the like.

The compositions of the present invention 15 include compositions such as suspensions, solutions, elixirs, aerosols, and solid dosage forms. Carriers such as starches, sugars, microcrystalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like, are commonly 20 used in the case of oral solid preparations (such as powders, capsules, and tablets), with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparation is tablets.

25 Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be coated by standard aqueous or nonaqueous techniques.

30 In addition to the common dosage forms set out above, the compounds of the present invention may

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also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos.: 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719; the disclosures of which 5 are hereby incorporated by reference.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosol sprays, each 10 containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared 15 by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately 20 admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

For example, a tablet may be prepared by 25 compression or molding, optionally, with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, 30 lubricant, inert diluent, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine, a mixture of the

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powdered compound moistened with an inert liquid diluent. Desirably, each tablet contains from about 0.5 mg to about 10 mg of the active ingredient. Most preferably, the tablet, cachet or capsule contains 5 either one of three dosages, about 0.5 mg, about 2 mg or about 8 mg of the active ingredient.

The invention is further defined by reference to the following examples describing in detail the preparation of the compositions of the present 10 invention, as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the purpose and interest of this invention.

15

#### TEST 1

A test for activity in lowering serum LDL and cholesterol is carried out according to the method of Havel et al. [Arteriosclerosis 2, 467-474 (1982)].

20 Homozygous Watanabe-heritable hyperlipidemic (WHHL) rabbits are maintained on Purina Rabbit Laboratory Chow and used at 3-5 months of age.

Blood is collected from the ear veins of unanesthetized rabbits or from the abdominal aorta of anesthetized rabbits and placed on ice. Lipoproteins 25 are separated from plasma by sequential ultracentrifugation. For analysis of lipoprotein composition and for separation of protein components, samples are recentrifuged at their upper density limits.

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Total cholesterol and triglycerides are estimated in plasma, and lipoprotein fractions by the automated technique of Rush et al. [Rush RL, Leon L, Turrell J. "Automated simultaneous cholesterol and 5 triglyceride determination on the autoanalyzer II instrument." In: Advances in Automated Analysis- Technicon International Congress-1970/Clinical Analysis. Mt. Kisco: Futura, 1970; 1:503-507] For measurements of lipoprotein composition, one can also 10 estimate free and esterified cholesterol, phospholipids, and protein.

#### TEST 2

A test for vascular dilatation is carried out as follows: New Zealand White rabbits, weighing 2.0 to 15 2.5 kg, are sacrificed by cervical dislocation and the thoracic aortas excised immediately. The aortas are then immersed in warm, oxygenated Krebsbicarbonate solution and cut in transverse or spiral strips, 1 to 3 mm in width. The strips are suspended 20 vertically in tissue baths containing an isotonic bicarbonate buffer. The composition of this buffer may be as follows (amount in millimoles per liter): NaCl, 119.0; KCl, 4.7; CaCl<sub>2</sub>, 2.5; MgSO<sub>4</sub>, 1.5; KH<sub>2</sub>PO<sub>4</sub>, 1.2; NaHCO<sub>3</sub>, 25.0; and dextrose, 11.0. The bathing 25 medium is aerated with 95% O<sub>2</sub> and 5% CO<sub>2</sub> and maintained at 37.0± 0.5° C and pH 7.4. The lower end of each strip is secured to a tissue holder and the upper end attached via a string or a fine chain to a force-displacement transducer; responses are 30 displayed on recorders. Tissues are placed under an initial tension of 0.1 to 2.0 g and permitted to stretch and equilibrate before testing. The tension

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on the strips is readjusted intermittently to the initial tension during the equilibration period. Drugs are introduced into the tissue baths with syringes or pipettes and removed by drainage and 5 replacement of the bathing medium from preheated, oxygenated reservoirs. Responses are expressed as gram changes in tension above base-line.

The response of the tissue to 1 $\mu$ g/mL phenylephrine is measured. The tissue is incubated 10 with varying concentrations of the test substances and the response to phenylephrine re-evaluated. Alternatively the tissues are precontracted with an  $\alpha$ -receptor stimulator such as phenylephrine and relaxed by gradual additions of a test substance to 15 the bath fluid.

#### TEST 3

The procedure analogous to the one described above is repeated using canine urethral tissue in place of rabbit aorta to determine potential urinary 20 tract effects.

#### TEST 4

A test for insulin resistance is carried out as an indication of favorable changes in serum lipid levels. Castelli, American Heart Journal, 112: 432-25 40 (1986) and McKeigne et al, British Heart Journal, 60: 390-96 (1988) have shown that insulin resistance and hyperinsulinemia lead to decreases in plasma HDL cholesterol concentrations and increases in plasma triglyceride levels. The beneficial effects of

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doxazosin on plasma lipids are therefore consistent with previous findings of a decreased insulin resistance in man after dosing with doxazosin, and a test protocol which measures insulin resistance 5 correlates with an expectation of similar responses in serum lipids in vivo.

Insulin is a hormone that activates various biochemical processes in the body, the most well known being facilitation of glucose transport over 10 cell membranes and activation of cell growth. The development of insulin resistance is common both in diabetics and nondiabetics, but it is only the glucose transport system that develops resistance to insulin. To compensate for the impaired glucose 15 transport, the normal body produces more insulin and the diabetic patient has to inject higher doses of insulin. Since insulin also is a growth hormone, the increased insulin concentration induces an accelerated growth of atherosclerotic lesions and 20 increased risk for cardiovascular morbidity and mortality.

The present studies are performed in old, spontaneously hypertensive rats (SHRs), which are known to develop insulin resistance. Racemic 25 doxazosin, (-) doxazosin, and (+) doxazosin are studied for their effects on glucose transport, insulin plasma concentration and arterial blood pressure.

Prior to receiving vehicle or test compound, 30 basal measurements of the following parameters are made: (1) systolic blood pressure (measured via tail

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cuff occlusion); (2) fasting levels of plasma insulin and triglycerides; and (3) glucose tolerance.

The SHRs receive vehicle or test compound via oral gavage once or twice daily for two or four weeks. Measurements of blood pressure, circulating insulin and triglycerides, and glucose clearance are made following two (and four) weeks of drug administration. Any changes in insulin resistance resulting from the drug treatment are evident as changes in the ratio of plasma glucose/plasma insulin levels and from the glucose tolerance tests.

#### TEST 5

A test for orthostatic hypotension and reflex tachycardia is carried out in dogs. Groups of dogs are tested with suitable doses of racemic doxazosin, (-) doxazosin, and (+) doxazosin and the effects on blood pressure (orthostatic hypotension) and heart rate (reflex tachycardia) are monitored and recorded at predetermined time intervals. Conscious normotensive dogs with surgically implanted arterial catheters are used to study the effects of the drugs on orthostatic hypotension and heart rate. The animals may also be equipped with cutaneous electrodes connected to suitable equipment for recording electrocardiograms. The tip of the indwelling catheter is positioned at the junction between the aorta and the left carotid artery. Blood pressure is measured by means of a pressure transducer and heart rate is computed from the systolic peaks in blood pressure or from the R-waves of the EKG. Doses of the test compounds are given

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orally or parenterally and the effects on the cardiovascular parameters are initially recorded with the animals in normal standing position. The animals are then held by their front paws and lifted into an upright position, standing on their hind paws. Drugs causing orthostatic hypotension will cause a sudden fall in recorded arterial blood pressure, sometimes accompanied by a reflex tachycardia.

EXAMPLE 1

10 ORAL FORMULATION

Capsules:

	Formula	Quantity per capsule in mg		
		A	B	C
15	(+) Doxazosin	0.5	2.0	8.0
	Lactose	84	82.5	76.5
	Cornstarch	15	15	15
	Magnesium Stearate	0.5	0.5	0.5
20	Compression Weight	100.0	100.0	100.0

The active ingredient, (+) doxazosin, is sieved and blended with the excipient. The mixture is filled into suitably sized two-piece hard gelatin capsules using suitable machinery. Other doses may be prepared by altering the fill weight and if necessary, changing the capsule size to suit.

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**EXAMPLE 2**  
**ORAL FORMULATION**

**Tablets:**

	<b>Formula</b>	<b>Quantity per tablet in mg</b>		
		<b>A</b>	<b>B</b>	<b>C</b>
	(+) Doxazosin	0.5	2.0	8.0
	Lactose	72.25	70.75	64.75
	Cornstarch	3.0	3.0	3.0
10	Water (per thousand Tablets)*	30.0 mL	30.0 mL	30.0 mL
	Cornstarch	18.75	18.75	18.75
	Magnesium Stearate	0.50	0.50	0.50
15	Compression Weight	125.0	125.0	125.0

\*The water evaporates during manufacture

The active ingredient is blended with the lactose until a uniform blend is formed. The smaller quantity of cornstarch is blended with the water to form the resulting cornstarch paste. This is then mixed with the uniform blend until a uniform wet mass is formed and the remaining cornstarch is added and mixed until uniform granules are obtained. The granules are screened through a suitable milling machine using a 1/4" stainless steel screen. The milled granules are dried in a suitable drying oven and milled through a suitable milling machine again. The magnesium stearate is then blended and the resulting mixture is compressed into tablets of desired shape, thickness, hardness and disintegration.

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What is claimed is :

1. A method of eliciting an increase in urine flow in a human which comprises administering to a human an amount of (+) doxazosin, or a pharmaceutically acceptable salt thereof,  
5 substantially free of its (-) stereoisomer, said amount being sufficient to increase urine flow.
2. The method of claim 1 wherein the human is in need of therapy for benign prostatic hyperplasia.
3. A method of eliciting an increase in urine flow in a human while avoiding the concomitant liability of hypotensive effects associated with racemic doxazosin, which comprises administering to a  
5 human an amount of (+) doxazosin, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to increase urine flow but insufficient to cause said hypotensive effects.
4. The method of claim 1 wherein (+) doxazosin is administered by intravenous infusion, transdermal delivery, or orally as a tablet or a capsule.
5. The method of claim 4 wherein the amount of (+) doxazosin or a pharmaceutically acceptable salt thereof administered is from about 0.1 mg to about 20 mg per day.
6. The method of claim 5 wherein the amount administered is from about 0.5 mg to about 10 mg per day.

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7. The method of claim 6 wherein the amount administered is from about 0.5 mg to about 5 mg per day.

8. The method of claim 1 wherein the amount of (+) doxazosin or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total weight of doxazosin.

9. The method of claim 1 wherein the amount of said (+) doxazosin or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, is administered together with a pharmaceutically acceptable carrier.

10. The method according to claim 1, wherein (+) doxazosin is administered as a salt selected from the group consisting of hydrochlorides and methane sulfonates.

11. A composition for increasing urine flow in a human which comprises an amount of (+) doxazosin or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to increase urine flow but insufficient to cause hypotensive effects associated with the administration of racemic doxazosin.

12. The composition according to claim 11 wherein the amount of (+) doxazosin is from about 0.1 mg to about 20 mg.

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13. The composition according to claim 12 wherein the amount of (+) doxazosin is from about 0.5 mg to about 10 mg.

14. The composition according to claim 11 wherein (+) doxazosin is present as a salt selected from the group consisting of hydrochlorides and methane sulfonates.

15. The composition according to claim 11 wherein said composition is adapted for oral administration.

16. The composition according to claim 11 adapted for parenteral delivery.

17. A composition according to claim 16 adapted for intramuscular delivery.

18. The composition according to claim 11 adapted for transdermal delivery.

19. The composition according to claim 11 wherein (+) doxazosin or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer is administered together with a pharmaceutically acceptable carrier.

20. A method of lowering plasma cholesterol and low density lipoprotein levels in a human which comprises administering to a human an amount of (+) doxazosin, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to lower said

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cholesterol and LDL levels.

21. The method of claim 20 wherein the human is in need of therapy for atherosclerosis.

22. A method of lowering plasma cholesterol and low density lipoprotein levels in a human while avoiding the concomitant liability of adverse effects associated with racemic doxazosin, which comprises  
5 administering to a human an amount of (+) doxazosin, or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, said amount being sufficient to lower said cholesterol and LDL levels but insufficient to cause said adverse  
10 effects.

23. The method of claim 20 wherein (+) doxazosin is administered by intravenous infusion, transdermal delivery, or orally as a tablet or a capsule.

24. The method of claim 23 wherein the amount of (+) doxazosin or a pharmaceutically acceptable salt thereof administered is from about 0.1 mg to about 20 mg per day.

25. The method of claim 24 wherein the amount administered is from about 0.5 mg to about 10 mg per day.

26. The method of claim 25 wherein the amount administered is from about 0.5 mg to about 5 mg per day.

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27. The method of claim 20 wherein the amount of (+) doxazosin or a pharmaceutically acceptable salt thereof is greater than approximately 90% by weight of the total weight of doxazosin.

28. The method of claim 20 wherein the amount of said (+) doxazosin or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer is administered together with a 5 pharmaceutically acceptable carrier.

29. The method according to claim 20 wherein (+) doxazosin is administered as a salt selected from the group consisting of hydrochlorides and methane sulfonates.

30. A composition for lowering serum cholesterol and low density lipoproteins in humans, which comprises an amount of (+) doxazosin or a pharmaceutically acceptable salt thereof, 5 substantially free of its (-) stereoisomer, said amount being sufficient to lower serum low density lipoproteins, but insufficient to cause adverse effects associated with the administration of racemic doxazosin.

31. The composition according to claim 30 wherein the amount of (+) doxazosin is from about 0.1 mg to about 20 mg.

32. The composition according to claim 31 wherein the amount of (+) doxazosin is from about 0.5 mg to about 10 mg.

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33. The composition according to claim 30 wherein (+) doxazosin is present as salt selected from the group consisting of hydrochlorides and methane sulfonates.

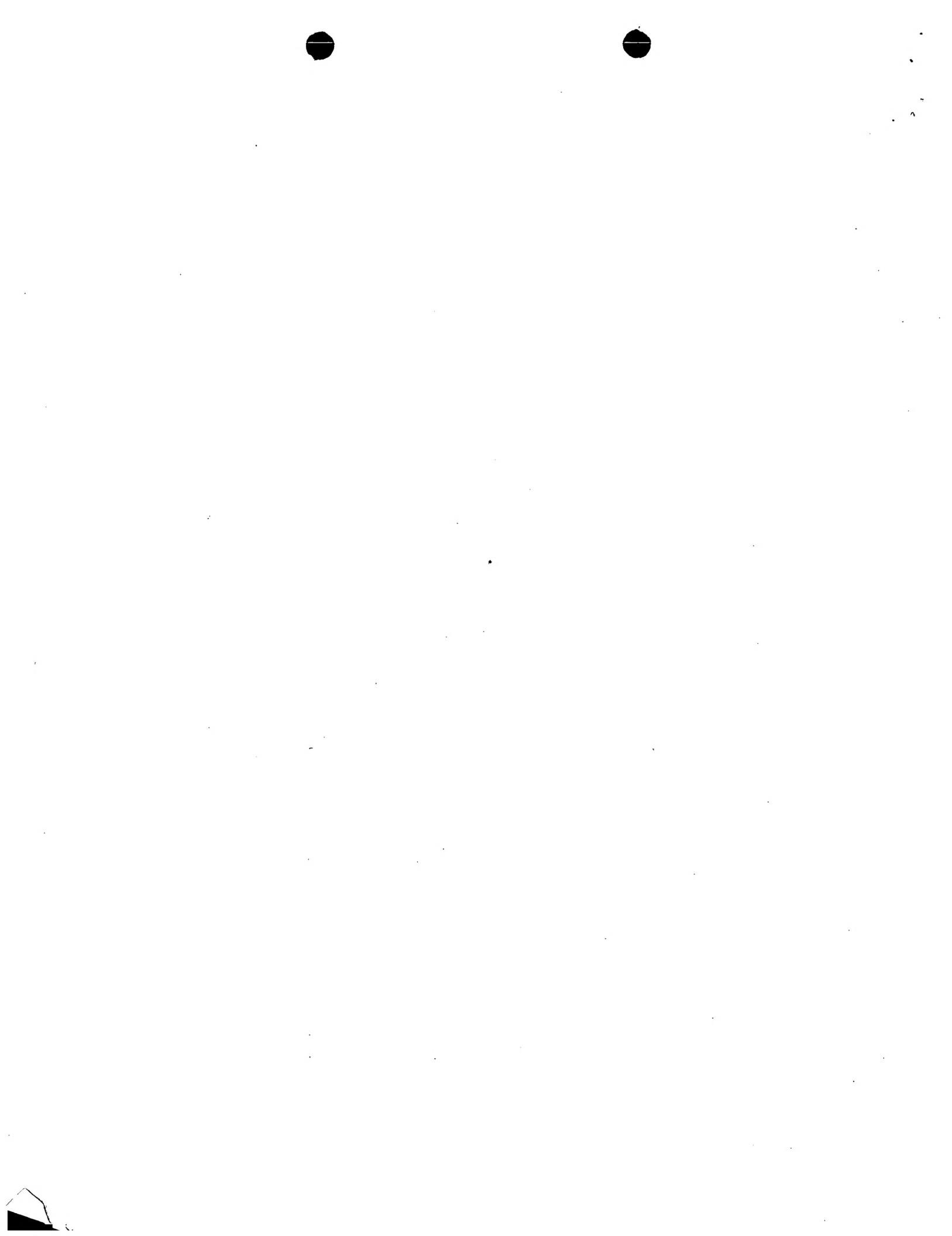
34. The composition according to claim 30 wherein said composition is adapted for oral administration.

35. The composition according to claim 30 adapted for parenteral delivery.

36. The composition according to claim 35 adapted for intramuscular delivery.

37. The composition according to claim 30 adapted for transdermal delivery.

38. The composition according to claim 30 wherein (+) doxazosin or a pharmaceutically acceptable salt thereof, substantially free of its (-) stereoisomer, is administered together with a  
5 pharmaceutically acceptable carrier.



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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> <b>PCT/US93/10503</b> <b>(22) International Filing Date:</b> <b>2 November 1993 (02.11.93)</b>  <b>(30) Priority data:</b> <b>07/970,685</b> <b>4 November 1992 (04.11.92)</b> <b>US</b>		<b>(81) Designated States:</b> AT, AU, BB, BG, BR, BY, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
<b>(71) Applicant:</b> SEPRACOR, INC. [US/US]; 33 Locke Drive, Marlborough, MA 01752 (US). <b>(72) Inventor:</b> GRAY, Nancy, M. ; 33 Locke Drive, Marlborough, MA 01752 (US). <b>(74) Agents:</b> HANSEN, Philip, E. et al.; Heslin & Rothenberg, 450 New Karner Road, P.O. Box 12695, Albany, NY 12205-12695 (US).		<b>(88) Date of publication of the international search report:</b> <b>4 August 1994 (04.08.94)</b>	
<b>(54) Title:</b> METHODS AND COMPOSITIONS OF (+) DOXAZOSIN FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA AND ATHEROSCLEROSIS			
<b>(57) Abstract</b> <p>Methods and compositions are disclosed utilizing the optically pure (+) isomer of doxazosin. This compound is a potent drug for the treatment of benign prostatic hyperplasia while avoiding the concomitant liability of hypotensive effects associated with the racemic mixture of doxazosin. The optically pure (+) isomer of doxazosin is also useful for the treatment and prevention of atherosclerosis and other conditions related to elevated serum LDL and cholesterol levels, such as coronary artery disease, without the concomitant liability of adverse effects associated with the racemic mixture of doxazosin.</p>			

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 93/10503

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 5 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	J.MED.CHEM. vol. 30, no. 1 , 1987 pages 49 - 57 S.F.CAMPBELL ET AL. '2,4-Diamino-6,7-dimethoxyquinazolines. 1. see the whole document ---	1-38
X	US,A,4 188 390 (CAMPBELL) 12 February 1980 cited in the application see column 3, line 13 - line 23 ---	1-38
X	SCHWEIZ.MED.WOCHENSCHR. vol. 120, no. 5 , 3 February 1990 pages 131 - 134 E.J.ARIENS 'STEREOSELECTIVITY IN PHARMACODYNAMICS AND PHARMACOKINETICS' see the whole document ---	1-38
-/--		

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

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- \*'&' document member of the same patent family

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Date of the actual completion of the international search

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Date of mailing of the international search report

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Name and mailing address of the ISA

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PHARMACEUTISCH WEEKBLAD vol. 125, no. 2 , 1 June 1990 pages 552 - 554 E.J.ARIENS 'RACEMISCHE THERAPEUTICA PROBLEEMMIDDELEN' see the whole document ---	1-38
X	CHIRALITY vol. 2 , 1990 pages 129 - 133 B.TESTA ET AL. 'RACEMATES VERSUS ENANTIOMERS IN DRUG DEVELOPMENT: DOGMATISM OR PRAGMATISM?' see the whole document ---	1-38
X	EUR.J.CLIN.PHARMACOL. vol. 41, no. 2 , 1991 pages 89 - 93 E.J.ARIENS 'RACEMIC THERAPEUTICS - ETHICAL AND REGULATORY ASPECTS' see the whole document ---	1-38
X,P	MED.MONATSSCHR. PHARM. vol. 15, no. 12 , December 1992 pages 362 - 364 S.HEINZL 'Prostataadenom: Neue Arzneimittel, neue Operationstechniken' see the whole document, especially page 364, right column, last three lines ---	1-19
X	PROSTATE vol. 16, no. 1 , 1990 pages 29 - 38 H.LEPOR ET AL. 'Binding and Functional Properties of Doxazosin in the Human Prostate Adenoma and Canine Brain' see the whole document ---	1-19
A	WO,A,92 16213 (MERCK & CO., INC.) 1 October 1992 see abstract ---	1-19
X	BIOCHEM.SOC.TRANS. vol. 20, no. 4 , November 1992 page 342S D.OWENS ET AL. 'The effect of alpha blockade on cholesterol regulation in vitro and in vivo' see the whole document ---	20-38
2		-/-

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 93/10503

## C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	AM.HEART J. vol. 121, no. 1PT2 , January 1991 pages 395 - 401 R.H.HERNANDEZ ET AL. 'Evidence of an antiplatelet aggregation action of doxazocin in patients with hypertension: An ex vivo study' see abstract ---	20-38
X	ATHEROSCLEROSIS vol. 91, no. 1-2 , November 1991 pages 35 - 49 M.C.KOWALA ET AL. 'Doxazocin and cholestyramine similarly decrease fatty streak formation in the aortic arch of hyperlipidemic hamsters' see abstract ---	20-38
X	J.HUM.HYPERTENS. vol. 4, no. SUP3 , October 1990 pages 23 - 33 J.L.POOL ET AL. 'Alphal-adrenoceptor blockade and the molecular basis of lipid metabolism alterations' see the whole document ---	20-38
X	DRUGS vol. 35, no. 5 , 1988 R.A.YOUNG ET AL. 'Doxazocin A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Efficacy in Mild or Moderate Hypertension' see the whole document -----	20-38

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US93/10503

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**REMARK:** Although claims 1-10 are directed to a method of treatment of the human/animal body, the search was based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. Method of eliciting an increase in urine flow, and compositions for use in this method (claims 1-19).
2. Method of lowering plasma cholesterol and low density lipoprotein levels, and compositions for use in this method (claims 20-38).

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest** The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

Serial Application No

PCT/US 93/10503

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4188390	12-02-80	AT-B- 366684 AT-B- 365186 AU-B- 509329 BE-A- 871771 CA-A- 1088059 CH-A- 643255 DE-A,C 2847623 FR-A,B 2407929 GB-A,B 2007656 JP-C- 1083043 JP-A- 54098792 JP-B- 56025233 LU-A- 80470 NL-A- 7810909 SE-B- 437518 SE-A- 7811382	26-04-82 28-12-81 08-05-80 03-05-79 21-10-80 30-05-84 23-05-79 01-06-79 23-05-79 29-01-82 03-08-79 11-06-81 05-06-80 08-05-79 04-03-85 06-05-79
WO-A-9216213	01-10-92	AU-A- 1751492 EP-A- 0576603	21-10-92 05-01-94

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